



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

10/552,299

08/25/2006

Orit Kollet

30694/41506

2069

4743

7590

03/01/2011

MARSHALL, GERSTEIN & BORUN LLP
233 SOUTH WACKER DRIVE
6300 WILLIS TOWER
CHICAGO, IL 60606-6357

EXAMINER

SHEN, WU CHENG WINSTON

ART UNIT

PAPER NUMBER

1632

NOTIFICATION DATE

DELIVERY MODE

03/01/2011

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mgbdoCKET@marshallip.com

Office Action Summary	Application No. 10/552,299	Applicant(s) KOLLET ET AL.	
	Examiner WU-CHENG Winston SHEN	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 December 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-62 is/are pending in the application.
- 4a) Of the above claim(s) 8, 10-29, 37 and 40-62 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7, 9, 30-36, 38 and 39 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 07 October 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Art Unit: 1632

DETAILED ACTION

The finality of the office action mailed on 01/20/2010 is withdrawn in view of the pre-appeal conference decision mailed on 08/24/2010. This is in response to Applicant's pre-appeal conference request filed on 07/06/2010. Prosecution on the merits resumes.

This application 10/552,299 filed on 08/25/2006 is a 371 of PCT/IL04/00314 filed on 04/07/2004, which claims the benefits of foreign applications ISRAEL 155302 filed on 04/08/2003 and ISRAEL 159306 filed on 12/10/2003.

Election/Restriction

In response to revised Restriction/Election mailed on 11/12/2010, Applicant's election with traverse of Group IX, drawn to claims 1-7, 9 (in part, pertaining to increasing level of chemoattractant receptor CXCR4 of the stem cells), 30-36, 38, and 39, drawn to a method of generating hematopoietic stem cells suitable for transplantation, the method comprising: (a) collecting stem cells; (b) exposing said stem cells to an exogenous matrix metalloprotease or an active portion thereof; and (c) isolating stem cells having increased CXCR4 levels compared to stem cells not exposed to the matrix metalloprotease or an active portion thereof, to thereby generate stem cells suitable for transplantation, in the reply filed on 12/10/2010 is acknowledged.

The traversal is on the ground(s) that Applicant incorporates the arguments found in the response filed March 6, 2009 to traverse the restriction requirement. The traversal is not found persuasive for the reasons documented on pages 2-3 of the office action mailed on 05/27/2009. With regard to election of species, as documented on pages 3-4 of the office action mailed on 05/27/2009, upon further consideration, the requirement for election of species between MMP-2

Art Unit: 1632

and MMP-9 recited in claim 33 is withdrawn because further search indicates that MMP-2 and MMP-9 are obvious variants to each other (See, for instance, **Skiles et al.**, The design, structure, and clinical update of small molecular weight matrix metalloproteinase inhibitors, Curr Med Chem. 11(22):2911-77, 2004).

Claims 1-62 are pending. Claims 8, 10-29, 37, and 40-62 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-7, 9, 30-36, 38, and 39, drawn to a method of generating hematopoietic stem cells suitable for transplantation, the method comprising: (a) collecting stem cells; (b) exposing said stem cells to an exogenous matrix metalloprotease or an active portion thereof; and (c) isolating stem cells having increased CXCR4 levels compared to stem cells not exposed to the matrix metalloprotease or an active portion thereof, to thereby generate stem cells suitable for transplantation are currently under examination to the extent of stem cells being hematopoietic stem cells, are currently under examination.

The requirement is still deemed proper and is therefore made FINAL

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Art Unit: 1632

1. Previous rejection of claims 30-36, 38, and 39 under 35 U.S.C. 103(a) as being unpatentable over **Kollet et al.** (Kollet et al., Rapid and efficient homing of human CD34(+) CD38(/low) CXCR4(+) stem and progenitor cells to the bone marrow and spleen of NOD/SCID and NOD/SCID/B2m(null) mice, Blood 97(10):3283-91, 2001; this reference is listed as reference C35 in the IDS filed by Applicant on 01/29/2007) in view of **Heissing et al.** (Heissing et al. Recruitment of stem and progenitor cells from the bone marrow niche requires MMP-9 mediated release of kit-ligand, Cell 109(5):625-37, 2002), **Togawa et al.** (Togawa et al., Highly activated matrix metalloproteinase-2 secreted from clones of metastatic lung nodules of nude mice injected with human fibrosarcoma HT1080, Cancer Lett. 146(1):25-33, 1999), **Rafii et al.** (US 2004/0071687, publication date 04/15/2004, filed on 05/28/2003, provisional application 60/383,658 file don 05/28/2002), and **Sadatmansoori et al.** (Sadatmansoori et al. Construction, Expression, and Characterization of a Baculovirally Expressed Catalytic Domain of Human Matrix Metalloproteinase-9, Protein Expr Purif. 23(3):447-52, 2001) is **withdrawn** because upon further consideration the rejection needs to be reformulated.

The following new grounds of 103(a) rejection is made of record upon further consideration of *Applicant's arguments*.

2. Claims 1-7, 9, 30-36, 38, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Rafii et al.** (US 2004/0071687, publication date 04/15/2004, filed on 05/28/2003, provisional application 60/383,658 filed on 05/28/2002) in view of **Fisher et al.** (Fisher et al., Engineering autoactivating forms of matrix metalloproteinase-9 and expression of the active enzyme in cultured cells and transgenic mouse brain, Biochemistry 41(26):8289-97, 2002), **Möhle et al.** (Möhle et al., The chemokine receptor CXCR-4 is expressed on CD34+ hematopoietic progenitors and leukemic cells and mediates transendothelial migration induced

Art Unit: 1632

by stromal cell-derived factor-1, Blood 91(12): 4523-30, 1998) and **Kollet et al.** (Kollet et al., Rapid and efficient homing of human CD34(+) CD38(low) CXCR4(+) stem and progenitor cells to the bone marrow and spleen of NOD/SCID and NOD/SCID/B2m(null) mice, Blood 97(10):3283-91, 2001; this reference is listed as reference C35 in the IDS filed by Applicant on 01/29/2007).

Claims 1 and 2 are directed to a method of increasing sensitivity of stem cells to a chemoattractant, the method comprising exposing the stem cells to a matrix metalloprotease or an active portion thereof, which is capable of increasing a level of at least one chemoattractant receptor of the stem cells to thereby increase the sensitivity of the stem cells to the chemoattractant, wherein said at least one chemoattractant receptor is CXCR4.

Claims 3 and 4 is recited to the method of claim 1, wherein said matrix metalloprotease is selected from the group consisting of MMP-2 and MMP-9.

Claim 5 is directed to the method of claim 1, wherein the stem cells are hematopoietic stem cells.

Claim 6 is directed to the method of claim 5, wherein said hematopoietic stem cells are CD34+ hematopoietic stem cells.

Claim 7 is directed to the method of claim 6, wherein said hematopoietic stem cells are CD34⁺/CD38^{low} hematopoietic stem cells.

Claim 9 is directed to the method of claim 1, wherein said exposing the stem cells to said matrix metalloprotease or said active portion thereof; is effected by: (i) expressing a polynucleotide encoding said matrix metalloprotease or an active portion thereof in the stem cells; and/or (ii) contacting the stem cells with said matrix metalloprotease or an active portion thereof.

Claim 30 is directed to a method of generating stem cells suitable for transplantation, the method comprising: (a) collecting stem cells; (b) exposing said stem cells to an exogenous matrix metalloprotease or an active portion thereof; and (c) isolating stem cells having increased

Art Unit: 1632

CXCR4 levels compared to stem cells not exposed to the matrix metalloprotease or an active portion thereof, to thereby generate stem cells suitable for transplantation.

Claim 31 is directed to the method of claim 30, wherein collecting said stem cells is effected by: (i) a stem cell mobilization procedure; and/or (ii) a surgical procedure.

Claim 32 and 33 are directed to the method of claim 30, wherein said matrix metalloprotease is selected from the group consisting of MMP-2 and MMP-9.

Claim 34 is directed to the method of claim 30, wherein said stem cells are hematopoietic stem cells.

Claim 35 is directed to the method of claim 34, wherein said hematopoietic stem cells are CD34⁺ hematopoietic stem cells.

Claim 36 is directed to the method of claim 34, wherein said hematopoietic stem cells are CD34⁺/CD38^{-low} hematopoietic stem cells.

Claim 38 is directed to the method of claim 30, wherein said exposing said stem cells to said exogenous matrix metalloprotease or said active portion thereof, is effected by: (i) expressing a polynucleotide encoding said matrix metalloprotease or said active portion thereof in said stem cells; and/or (ii) contacting said stem cells with said matrix metalloprotease or said active portion thereof.

Claim 39 is directed to the method of claim 30, wherein said isolating stem cells having increased CXCR4 levels compared to stem cells not exposed to the matrix metalloprotease or an active portion thereof is effected by FACS.

With regard to limitation “collecting stem cells” recited in step (a) of claim 30, **Raffi et al.** teaches that the stem cells can be hematopoietic stem cells, endothelial stem cells, hepatic stem cells, neuronal stem cells, muscle stem cells or a combination thereof. The quiescent non-cycling stem cells are often in contact with bone marrow stromal cells, including osteoblasts and/or are generally maintained in a G₀ phase of cell cycle. The quiescent non-cycling stem cells can be Lin⁻Sca⁺c-Kit⁺ hematopoietic stem cells, VEGFR2⁺c-Kit⁺ endothelial stem cells,

Art Unit: 1632

VEGFR2⁺ vascular stem cells or AC133⁺ organ-specific stem cells (See paragraph [0017], Rafii et al., 2004). Rafii et al. teaches that S-phase Lin⁻Sca-1⁺c-Kit⁺ stem cells, isolated by a combination of magnetic cell isolation (MACS) and flow cytometry (FACS) (See paragraph [0027], Rafii et al., 2004).

With regard to the limitation “exposing said stem cells to an exogenous matrix metalloprotease or an active portion thereof” recited claim 1 and in step (b) of claim 30, the limitation “wherein said exposing said stem cells to said exogenous matrix metalloprotease or said active portion thereof, is effected by: (i) expressing a polynucleotide encoding said matrix metalloprotease or said active portion thereof in said stem cells; and/or (ii) contacting said stem cells with said matrix metalloprotease or said active portion thereof” recited in claims 9 and 38, **Rafii et al.** (US 2004/0071687) teaches endothelial-active cytokines, such as VEGF, and SDF-1 and their role in inducing mobilization of bone marrow repopulating cells, and MMPs are necessary intermediates downstream of these factors. Cytokine-induced mobilization of hematopoietic progenitors and cells with hematopoietic stem cell potential was markedly impaired in MPI-treated or MMP-9^{-/-} mice (See paragraph [0107], US 2004/0071687). Rafii et al. further teaches that MMP-9 promotes release of stem cell active cytokines, thereby promoting expansion of quiescent stem cells, and this novel concept lays the foundation of developing strategies where activation of proteases such as MMP-9 may act as molecular switches to expand a large population of stem cells that may ultimately be used for organ-regeneration and tissue vascularization (See paragraph [0114], and Figure 16, shown below, US 2004/0071687). Rafii et al. demonstrated that MMP-9-mediated release of sKitL is essential for promoting stem

Art Unit: 1632

cell differentiation, accelerating hematopoietic reconstitution following bone marrow ablation

(See paragraph [0197], US 2004/0071687).

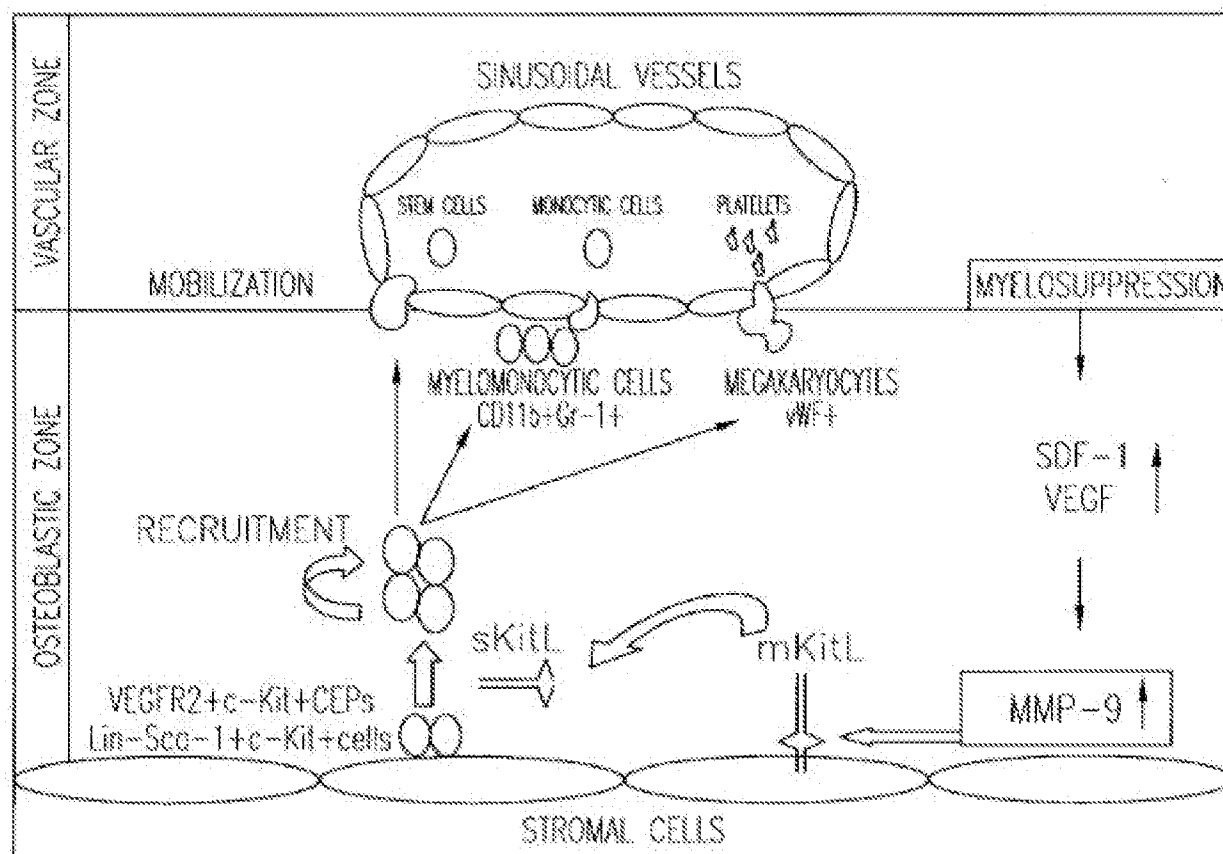


FIG. 16: a schematic diagram of the recruitment process. Under steady-state conditions quiescent c-Kit⁺ hematopoietic stem cells and CEPs reside in a niche in close contact with stromal cells, including osteoblasts. Membrane-bound cytokines such as mKitL not only convey survival signals, but also support the adhesion of stem cells to the stroma. Bone marrow ablation or chemokine/cytokine administration induces up-regulation of MMP-9 resulting in the release of sKitL. sKitL provides signals that enhances mobility of VEGFR2⁺ endothelial progenitors (CEPs) and Lin⁻Sca-1⁺c-Kit⁺ repopulating cells, translocating them into a vascular-enriched niche favoring differentiation and mobilization to the peripheral circulation.

Art Unit: 1632

With regard to the expression of a polynucleotide encoding a gene of interest in stem cells, Rafii et al. teaches that in vivo gene transfer using a biological means can be accomplished by administering the virus containing the DNA to the mammalian subject either by an oral route, or by injection depending upon the tissue targeted for gene transfer. For example, where the targeted cells are stem cells and where a virus containing the DNA of interest is administered into the bone marrow, the virus will be administered at a concentration effective to infect bone marrow cells of the mammalian subject and provide for expression of the nucleic acid sequence at levels sufficient to recruit stem or progenitor cells from the bone marrow (See paragraph [0130], US 2004/0071687). It is worth noting that Rafii et al. teaches that bone marrow not only provides a suitable micro-environment for hematopoietic stem cells, but is also a dispensable reservoir for organ-specific stem cells for endothelium, muscle, brain, pancreas, and liver cells (See paragraph [0109], US 2004/0071687).

Rafii et al. does not explicitly teach the expression of exogenous MMP protein from a polynucleotide or addition of exogenous matrix metalloproteinase (MMP) or active portion thereof. In this regard, **Fisher et al.** teaches engineering wild type and various mutant autoactivating forms of matrix metalloproteinase-9 and expression of the active enzyme in cultured cells and transgenic mouse brain to evaluate the effect of increased levels of active MMP-9 in the central nervous system (See title and abstract, Fisher et al., 2002). It is noted that MMP-9 is a downstream effector of SDF-1 mediated molecular signaling of stem cell mobilization (See Figure 16, Rafii et al.), accordingly, it is prima facie obvious that the up-regulation of MMP-9 taught by Rafii can be achieved by the exogenous expression of active MMP-9 enzyme from an expression vector taught by Fisher et al. It is further noted that the

Art Unit: 1632

breadth of claimed methods reciting an open language “comprising”, which does not exclude the embodiment with additional step of “bone marrow ablation or chemokine/cytokine administration” that up-regulates MMP-9 expression taught by Rafii et al.

The combined teachings of Rafii et al. and Fisher et al. do not explicitly teach mobilized stem cell having increased CXCR4 levels recited in claims 1, 2, 30 and 39, and the expression of markers of mobilized hematopoietic stem cells recited in claims 5-7 and 34-36.

With regard to the limitations mobilized stem cell having increased CXCR4 levels recited in claims 1, 2, 30 and 39, **Möhle et al.** teaches the chemokine receptor CXCR-4 is expressed on CD34+ hematopoietic progenitors and leukemic cells and mediates transendothelial migration induced by stromal cell-derived factor-1 (See title, Möhle et al.). Möhle et al. teaches that chemokine stromal cell-derived factor-1 (SDF-1) and its receptor CXCR-4 are likely to be involved in the trafficking of hematopoietic progenitor and stem cells, as suggested by the reduced bone marrow hematopoiesis in SDF-1-deficient mice and the chemotactic effect of SDF-1 on CD34+ progenitor cells. Migration of leukemic cells might also depend on the expression of chemokine receptors. Möhle et al. concludes that CXCR-4 is expressed on CD34+ cells including more primitive, pluripotent progenitors, and may therefore play a role in the homing of hematopoietic stem cells. CXCR-4 expressed in variable amounts on primary AML leukemic cells is functionally active and may be involved in the trafficking of malignant hematopoietic cells (See abstract, Mohle et al., 1998).

With regard to the limitations the expression of markers of mobilized hematopoietic stem cells recited in claims 5-7 and 34-36, **Kollet et al.** teaches isolation of CD34+ hematopoietic

Art Unit: 1632

stem cells from human cord blood (CB) sample using the MACS cell isolation kit and MidiMac columns. Isolated CD34⁺ cells were either used immediately for homing experiments or after overnight incubation with RPMI supplemented with 10% fetal calf serum (FCS) and stem cell factor (SCF) (50 ng/mL). In both cases only **primitive CD34⁺CD38^{-low} cells homed in vivo**. (See Materials and methods, left column, page 3284, Kollet et al., 2001). Kollet et al. teaches that ex vivo cytokine-stimulated CB (cord blood) CD34⁺CD38⁺ cells had **increased CXCR4 expression** as well as improved migration capacities toward a gradient of SDF-1 and also could transiently home to the BM of NOD/SCID mice. **Primitive CD34⁺CD38^{-low} cells express higher levels of CXCR4** compared to CD34⁺CD38^{+high} cells (See bridging paragraph pages 3288-3289, Kollet et al., 2001).

Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Rafii et al. regarding activation of proteases such as MMP-9 may act as molecular switches to expand a large population of stem cells for stem cell recruitment/homing, and MMP-9-mediated release of sKitL is essential for promoting stem cell differentiation, accelerating hematopoietic reconstitution following bone marrow ablation, with the teachings of (i) Fisher et al. regarding engineering wild type and various mutant autoactivating forms of human matrix metalloproteinase-9 and expression of the active enzyme in cultured cells and transgenic mouse brain, (ii) Möhle et al. regarding the chemokine receptor CXCR-4 is expressed on CD34⁺ hematopoietic progenitors and leukemic cells and mediates transendothelial migration induced by stromal cell-derived factor-1, and (iii) Kollet et al. regarding primitive CD34⁺CD38^{-low} cells homed in vivo, and ex vivo cytokine-stimulated CB (cord blood) CD34⁺CD38⁺ cells had increased CXCR4 expression as well as

Art Unit: 1632

improved migration capacities toward a gradient of SDF-1 and also could transiently home to the BM of NOD/SCID mice, and primitive $CD34^+CD38^{-/low}$ cells express higher levels of CXCR4 compared to $CD34^+CD38^{+/high}$ cells, to arrive at the methods recited in claims 1-7, 9, 30-36, 38, and 39 of instant application.

One having ordinary skill in the art would have been motivated to combine the teachings of Rafii et al., Fisher et al., Möhle et al., Kollet et al. because (i) Rafii et al. teaches the roles of endothelial-active cytokines, such as VEGF, and SDF-1 in inducing mobilization of bone marrow repopulating cells, and MMPs are necessary intermediates downstream of these factors; furthermore, MMP-9 promotes release of stem cell active cytokines, thereby promoting expansion of quiescent stem cells, and activation of MMP-9 may act as molecular switches to expand a large population of stem cells, and (ii) Fisher et al. teaches technical details regarding engineering wild type and various mutant autoactivating forms of matrix metalloproteinase-9 and expression of the active enzyme in cultured cells and transgenic mouse, (iii) Möhle et al. teaches that chemokine stromal cell-derived factor-1 (SDF-1) and its receptor CXCR-4 are likely to be involved in the trafficking of hematopoietic progenitor and stem cells, and (iv) Kollet et al. teaches detailed characterization of marker expression that primitive $CD34^+CD38^{-/low}$ cells homed in vivo, and ex vivo cytokine-stimulated CB (cord blood) $CD34^+CD38^+$ cells had increased CXCR4 expression as well as improved migration capacities toward a gradient of SDF-1 and also could transiently home to the BM of NOD/SCID mice. Moreover, primitive $CD34^+CD38^{-/low}$ cells express higher levels of CXCR4 compared to $CD34^+CD38^{+/high}$ cells primitive $CD34^+CD38^{-/low}$ cells homed in vivo.

Art Unit: 1632

There would have been a reasonable expectation of success given (i) the establishment of MMP-9 promotes release of stem cell active cytokines, thereby promoting expansion of quiescent stem cells, and activation of MMP-9 may act as molecular switches to expand a large population of stem cells, and the role of SDF-1 in inducing mobilization of bone marrow repopulating cells, by the teachings of Rafii et al., (ii) successful demonstration of genetic engineering wild type and various mutant autoactivating forms of human matrix metalloproteinase-9 and expression of the active enzyme in cultured cells and transgenic mouse, by the teachings of Fisher et al., (iii) the establishment of chemokine stromal cell-derived factor-1 (SDF-1) and its receptor CXCR-4 interaction involved in regulating the trafficking of hematopoietic progenitor and stem cells, by the teachings of Möhle et al., and (iv) successful demonstration of primitive CD34⁺CD38^{-/low} cells homed in vivo, and ex vivo cytokine-stimulated CB (cord blood) CD34⁺CD38⁺ cells had increased CXCR4 expression as well as improved migration capacities toward a gradient of SDF-1 and also could transiently home to the BM of NOD/SCID mice, by the teachings of Kollet et al.

Thus, the claimed invention as a whole was clearly prima facie obvious

The Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.* that forecloses the argument that a **specific** teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR*, 82 USPQ2d at 1936) [available at <http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf>; and *KSR Guidelines Update* has been published in the Federal Register at 75 Fed. Reg. 53643-60 (Sep. 1, 2010) and is posted at USPTO's internet Web site at <http://www.uspto.gov/patents/law/notices/2010.jsp>]. The

Art Unit: 1632

Examiner notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.*, the suggestion and motivation to combine Rafii et al., Fisher et al., Möhle et al., Kollet et al. has been clearly set forth above in this office action.

It is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant's arguments

Applicant's remarks filed on 03/17/2010 regarding the previous rejection of record are addressed as the related to the new grounds of rejection set forth above in this office action.

Conclusion

3. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Art Unit: 1632

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/

Primary Examiner

Art Unit 1632